Exhibit 1

Patents

Method for synthesizing diovan

Abstract

The present invention provides an improved method used for synthesizing valsartan. No tin compounds are required in the reaction. In the method, the condensate of N-[(2'-cyano-1, 1'-biphenyl-4-group)-alkyl]-L-valine ester is used as raw material. And the method comprises valerylation and synthesis of the valsartan. The method has the advantages of easily available raw materials, simple operation, no environmental pollution, high yield, low cost, and suitability for large-scale industrial production.

CN101270096B

China

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Other languages: Chinese

Inventor: 王礼权, 陈伟, 刘大鹏

Current Assignee : Zhejiang Huahai Pharmaceutical Co Ltd

Worldwide applications

2007 CN

Application CN2007100383460A events

2007-03-22	Application filed by Zhejiang Huahai Pharmaceutical Co Ltd
2007-03-22	Priority to CN2007100383460A
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2011-08-03	Application granted
2011-08-03	Publication of CN101270096B
Status	Active
2027-03-22	Anticipated expiration

Info: Non-patent citations (1), Cited by (9), Legal events, Similar documents, Priority and Related Applications

External links: Espacenet, Global Dossier, Discuss

Claims (7)

Hide Dependent

1. the method for a synthesizing Xieshatan is characterized in that this method comprises the following steps:

(1) aqueous solution with the aromatic solvents of compound 3 and 0.5 ~ 10 times of weight and carbonate is even, controlled temperature is at 0 ~ 30 ℃ of mixture that begins to drip 0.4 ~ 0.8 times of weight valeryl chloride and 1 ~ 10 times of weight aromatic solvents, 0.5 dripped and finish in ~ 4 hours, keeping 10 ~ 40 ℃ stirred 1 ~ 3 hour, branch vibration layer, organic layer saturated common salt water washing, penta acylate solution is directly used in follow-up syntheticly or boil off partial solvent, it is standby to separate out compound 2;

(2) use the compound 2 that goes on foot preparation and be dissolved in toluene; to the metal-salt of the hydrazoic acid that wherein adds 0.5 ~ 4.0 times of penta acylate amount of substance and the triethylamine hydrochloride of 0.5 ~ 2.0 times of amount of substance; stir; be heated to 70 ~ 150 ℃; back flow reaction 10 ~ 50 hours; reaction finishes postcooling to room temperature; add the saturated common salt water washing, organic layer adds the aqueous solution of 10% ~ 30% alkali again, and controlled temperature was 0 ~ 40 ℃ of reaction 4 ~ 10 hours; divide and remove organic layer; add an amount of aromatic solvents washing to the alkali layer, be cooled to below 0 ℃, regulate pH value 1 ~ 2 with hydrogen chloride solution; use ethyl acetate extraction; organic layer saturated common salt water washing boils off the part ethyl acetate, the cooling precipitation and crystallization; filter, get compound 1:

In the following formula: compound 1 is N-(1-pentanoyl)-N-[4-[2-(1H-tetrazole-5-yl) phenyl] benzyl]-the L-Xie Ansuan, wherein R is hydrogen, methyl, ethyl, sec.-propyl or benzyl; When R is H, be valsartan;

Compound 2 is N-(1-pentanoyl)-N-[4-[2-(5-cyano group) phenyl] benzyl]-L-Xie Ansuan alkyl ester, wherein R is hydrogen, methyl, ethyl, sec.-propyl or benzyl;

Compound 3N-[(2 '-cyano group-1,1 '-biphenyl-4-yl) alkyl]-L-L-valine ester hydrochloride, wherein R is hydrogen, methyl, ethyl, sec.-propyl or benzyl.

2. by the method for the described a kind of synthesizing Xieshatan of claim 1, it is characterized in that the metal-salt of step (2) hydrazoic acid is a sodium azide, nitrine potassium or nitrine lithium.

3. by the method for the described a kind of synthesizing Xieshatan of claim 1, it is characterized in that the preferred toluene of described solvent.

4. by the method for the described a kind of synthesizing Xieshatan of claim 1, it is characterized in that step (2) reaction is to carry out in 70 ~ 150 ℃ temperature range.

5. by the method for the described a kind of synthesizing Xieshatan of claim 1, formula 1 compound that it is characterized in that step (2) preparation can carry out ester hydrolysis reaction without separation and obtain valsartan.

6. press the method for the described a kind of synthesizing Xieshatan of claim 1, it is characterized in that this method comprise by formula 3 compounds and valeryl chloride in aromatic solvents in the presence of the aqueous solution of carbonate reaction obtain formula 2 compounds, after separating carbonate and acid salt thereof, formula 2 compounds do not need to separate from solvent, are directly used in preparation formula 1 compound.

7. in accordance with the method for claim 6, described solvent is toluene, parachlorotoluene or dimethylbenzene.

Description

A kind of method of synthesizing Xieshatan

Technical field

The invention belongs to technical field of pharmaceuticals.Be specifically related to improving one's methods of a kind of synthesizing Xieshatan that participates in reaction without tin compound.

Background technology:

Valsartan is the hypertensive chemical synthetic drug of a kind of effective treatment, its chemical name: (S) .N-(1-oxo amyl group)-N-[4-[2-(1H-tetrazole-5-yl) phenyl] benzyl]-the L-Xie Ansuan, English name (S)-N-pentanoyl-N-[[2 '-(1H-tetrazole-5-yl) [1,1 '-biphenyl]-4-yl] methyl]-L-valine (valsartan), its synthetic method mainly be divided into condenses (N-[(2 '-cyano group-1,1 '-biphenyl-4-yl) alkyl]-the L-L-valine ester) synthetic (containing the ester protection) of (hydrochloride), synthetic (containing valerylization) two parts of valsartan; The synthetic main route of condenses mainly contains: the one, with 2-cyano group-4 '-bromomethylbiphenyl is a raw material, get with carboxyl protected L-Xie Ansuan condensation, the 2nd, with 2-cyano group-4 '-formyl biphenyl is that raw material and the protected L-Xie Ansuan of carboxyl condensating reductive get; The synthetic of valsartan is raw material with condenses and sodium azide substantially all, in reaction under the catalysis that haloalkyl tin is arranged more than 40 hours and get.Owing to adopted stanniferous reagent, residual tin can take in the final product always, and organo-tin compound is the very strong compound of a kind of toxicity.According to medicine ICH requirement, organo-tin compound should be very difficult to control in 1ppmm in finished product.The relevant patent and the document of concrete reference, as US5399578, J.Med.Chem.1991, Vol.34, No.8,2525-2547 etc.

Summary of the invention:

Technical problem to be solved by this invention is to overcome the shortcoming of above-mentioned valsartan synthesis step, cancellation uses the haloalkyl tin compound to participate in reaction, the improved valsartan new synthetic method of research and design, the total recovery of raising valsartan, reduce and produce and raw materials cost, reduce environmental pollution.

The invention provides a kind of improvement synthetic method of synthesizing Xieshatan, to achieve the object of the present invention, it is raw material that the present invention adopts with the condenses, after the valeryl reaction, finishes the synthetic of valsartan without tin compound participates in reaction.

1:N-(1-pentanoyl)-N-[4-[2-(1H-tetrazole-5-yl) phenyl] benzyl]-L-Xie Ansuan (R is acceptable substituting groups such as hydrogen, methyl, ethyl, sec.-propyl or benzyl)

2:N-(1-pentanoyl)-N-[4-[2-(5-cyano group) phenyl] benzyl]-L-Xie Ansuan alkyl ester (R is acceptable substituting groups such as hydrogen, methyl, ethyl, sec.-propyl or benzyl)

3:N-[(2 '-cyano group-1,1 '-biphenyl-4-yl) alkyl]-L-L-valine ester hydrochloride (R is acceptable substituting groups such as hydrogen, methyl, ethyl, sec.-propyl or benzyl)

Concrete grammar of the present invention is: (1) is with N-[(2 '-cyano group-1,1 '-biphenyl-4-yl) alkyl]-aromatic solvents of L-L-valine ester (abbreviation condenses) (hydrochloride) and 0.5 ~ 10 times of weight and the aqueous solution of carbonate are even, controlled temperature is at 0 ~ 30 ℃ of mixture that begins to drip 0.4 ~ 0.8 times of weight valeryl chloride and 1 ~ 10 times of weight aromatic solvents, 0.5 dripped and finish in ~ 4 hours, keeping 10 ~ 40 ℃ stirred 1 ~ 3 hour, branch vibration layer, organic layer saturated common salt water washing, penta acylate solution is directly used in follow-up syntheticly or boil off partial solvent, it is standby to separate out penta acylate solid; (2) use penta acylate solution of step preparation or the solution that penta acylate solid is dissolved in the solvent of identical with step (1) solvent for use (also can be different); 0.5 the amine salt of the metal-salt of ~ 4.0 times of amount of substance hydrazoic acid and 0.5 ~ 2.0 times of amount of substance or other Lewis acids; stir; be heated to 70 ~ 150 ℃; back flow reaction 10 ~ 50 hours; reaction finishes postcooling to room temperature; add the saturated common salt water washing, organic layer adds the aqueous solution of 10% ~ 30% alkali again, and controlled temperature was 0 ~ 40 ℃ of reaction 4 ~ 10 hours; divide and remove organic layer; add an amount of aromatic solvents washing to the alkali layer, be cooled to below 0 ℃, regulate pH value 1 ~ 2 with hydrochloride aqueous solution; use ethyl acetate extraction; organic layer saturated common salt water washing boils off the part ethyl acetate, the cooling precipitation and crystallization; filter, get valsartan.

In the method for the invention, described condenses N-[(2 '-cyano group-1,1 '-biphenyl-4-yl) alkyl]-alkyl in the L-L-valine ester is acceptable substituting groups such as methyl, ethyl, sec.-propyl or benzyl, aromatic solvents is a toluene, acceptable all kinds of SOLVENTS such as parachlorotoluene or dimethylbenzene, preferred toluene or parachlorotoluene; The usage quantity of solvent is 1.5 ~ 20 times of condenses (hydrochloride) weight, preferred 10 times; Carbonate is yellow soda ash, salt of wormwood, sodium bicarbonate or saleratus etc.; The metal-salt of hydrazoic acid comprises sodium azide, nitrine potassium, nitrine lithium etc., amine salt or other Lewis acids are triethylamine salt, methylamine salt, organic salt and ammonium chlorides such as ethylenediamine salt or tert-butylamine salt, zinc chloride, inorganic salt such as ferrous sulfate, amine salt or other lewis acidic acid groups are the salt acid group, sulfate radical, inorganic acid radical and oxalic acid roots such as nitrate radical, oxalate, organic acids such as tosic acid root, the best is a triethylamine hydrochloride.Two steps of synthesizing Xieshatan that relate to the valerylization of step and the step (2) of above-mentioned steps (1) among the present invention; reaction solvent all can be selected toluene for use; acceptable all kinds of SOLVENTS such as parachlorotoluene or dimethylbenzene; two steps can be selected identical or different solvent for use; be preferably and select for use with a kind of solvent, the best is a toluene.

Method yield height of the present invention, calculating total recovery with condenses can be greater than 75%, and has following remarkable advantage:

1) valsartan improved need not cost an arm and a leg in synthetic and also corrodibility extremely strong, easily environment is caused the organotin halogenide of bigger harm, avoided fundamentally that residual heavy metal tin exceeds standard in the product.

2) two-step reaction selects for use price relatively cheap and reclaim easy solvent, and can be with the one kettle way synthesizing Xieshatan, can not switch solvent midway, indivedual in addition solvents have good promoter action for reaction, make solvent such as adopting parachlorotoluene, reaction times was shortened in 10 hours, improved working efficiency greatly.Help large-scale production

Embodiment:

Example 1

Add the 50L tap water, add 25kg salt of wormwood again and be stirred to molten clearly, add 20kg condenses hydrochloride and 150L toluene again, be stirred to molten clear.Controlled temperature begins to drip 9kg valeryl chloride and 25L toluene mixture liquid at 20 ~ 30 ℃, dropwises in about 2 hours, and holding temperature was 20 ~ 30 ℃ of stirring reactions 1 hour again, and standing demix divides the sub-cloud water layer, and organic layer adds the saturated common salt water washing again.Divide and remove the salt water layer, organic layer (penta acylate solution) is stand-by.Use penta acylate solution of step preparation, add sodium azide 7.3Kg again, triethylamine hydrochloride 17.8kg stirs, and is heated to backflow, react 20 hours, and the end postcooling to 30 ℃ of refluxing adds saturated aqueous common salt 50L, standing demix again.Dividing goes salt water layer, organic layer to use an amount of saturated common salt water washing again.Organic layer adds 13%KOH solution 180L again, and controlled temperature divides and removes organic layer 40 ℃ of reactions 4 hours.The alkali layer adds an amount of toluene wash again, divides and removes toluene layer.Be cooled to 0 ℃, drip the hydrochloric acid of 6N again, regulate pH value 1 ~ 2.Add ethyl acetate 400ml again and extract branch vibration layer.Organic layer adds saturated common salt water washing, layering again.Holding temperature is at 40 ℃, and decompression steams the part ethyl acetate, is cooled to precipitation and crystallization below-5 ℃ 12 hours, filters, and oven dry gets the product valsartan,, yield 78%.

Example 2

Replace outside the salt of wormwood in the example 1 with yellow soda ash, all the other are with example 1, yield 75%.

Example 3

Outside the salt of wormwood in the sodium bicarbonate replacement example 1, all the other are with example 1.

Example 4

Outside the salt of wormwood in the saleratus replacement example 1, all the other are with example 1.

Example 5

Aromatic solvents toluene in the example 1 is changed into outside the parachlorotoluene, and all the other are with example 1.

Example 6

Aromatic solvents toluene in the example 1 is changed into outside the dimethylbenzene, and all the other are with example 1.

Example 7

Except that sodium azide changed nitrine potassium into, all the other were with example 1.

Example 8

Except that sodium azide changed the nitrine lithium into, all the other were with example 1.

Example 9

Change triethylamine hydrochloride into triethylamine vitriol, all the other are with example 1.

Example 10

Change triethylamine hydrochloride into ethylenediamine-hydrochloride, all the other are with example 1.

Example 11

Change triethylamine hydrochloride into the tert-butylamine salt hydrochlorate, all the other are with example 1.

Example 12

Change triethylamine hydrochloride into ammonium chloride, all the other are with example 1.

Example 13

Change triethylamine hydrochloride into zinc chloride, all the other are with example 1.

Example 14

Aromatic solvents toluene in the example 2 is changed into outside the parachlorotoluene, and all the other are with example 2.

Example 15

Aromatic solvents toluene in the example 2 is changed into outside the dimethylbenzene, and all the other are with example 2.

Example 16

Except that sodium azide changed nitrine potassium into, all the other were with example 2.

Example 17

Except that sodium azide changed the nitrine lithium into, all the other were with example 2.

Example 18

Change triethylamine hydrochloride into zinc chloride, all the other are with example 2.

Example 19

Aromatic solvents toluene in the example 3 is changed into outside the parachlorotoluene, and all the other are with example 3.

Example 20

Aromatic solvents toluene in the example 3 is changed into outside the dimethylbenzene, and all the other are with example 3.

Example 21

Except that sodium azide changed nitrine potassium into, all the other were with example 3.

Example 22

Change triethylamine hydrochloride into ammonium chloride, all the other are with example 3.

Example 23

Change triethylamine hydrochloride into zinc chloride, all the other are with example 3.

Example 24

Aromatic solvents toluene in the example 4 is changed into outside the parachlorotoluene, and all the other are with example 4.

Example 25

Aromatic solvents toluene in the example 4 is changed into outside the dimethylbenzene, and all the other are with example 4.

Example 26

Except that sodium azide changed nitrine potassium into, all the other were with example 4.

Example 27

Except that sodium azide changed the nitrine lithium into, all the other were with example 4.。

Example 28

Change triethylamine hydrochloride into ammonium chloride, all the other are with example 4.

Example 29

Change triethylamine hydrochloride into zinc chloride, all the other are with example 4.

Example 30

Except that sodium azide changed nitrine potassium into, all the other were with example 5.

Example 31

Except that sodium azide changed the nitrine lithium into, all the other were with example 5.

Example 32

Change triethylamine hydrochloride into ammonium chloride, all the other are with example 5.

Example 33

Change triethylamine hydrochloride into zinc chloride, all the other are with example 5.

Example 34

Change triethylamine hydrochloride into iron protochloride, all the other are with example 5.

Example 35

Except that sodium azide changed nitrine potassium into, all the other were with example 6.

Example 36

Except that sodium azide changed the nitrine lithium into, all the other were with example 6.

Example 37

Change triethylamine hydrochloride into triethylamine vitriol, all the other are with example 6.

Example 38

Change triethylamine hydrochloride into ammonium chloride, all the other are with example 6.

Example 39

Change triethylamine hydrochloride into zinc chloride, all the other are with example 6.

Example 40

Change triethylamine hydrochloride into iron protochloride, all the other are with example 6.

Example 41

Change triethylamine hydrochloride into ammonium chloride, all the other are with example 7.

Example 42

Change triethylamine hydrochloride into zinc chloride, all the other are with example 7.

Example 43

Change triethylamine hydrochloride into iron protochloride, all the other are with example 7.

Example 44

Except that sodium azide changed nitrine potassium into, all the other were with example 37.

Example 45

Except that sodium azide changed the nitrine lithium into, all the other were with example 37.

Non-Patent Citations (1)

Title
贾庆忠等.抗高血压药缬沙坦的合成.中国医药工业杂志.2001,32(9),385-387. *

* Cited by examiner, † Cited by third party

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Publication number	Priority date	Publication date	Assignee	Title
Family To Family Citations				
EP2556059B1 *	2010-04-07	2014-05-07	KRKA, d.d., Novo mesto	Improved process for preparing valsartan
CN101817795B *	2010-05-13	2013-03-27	浙江美诺华药物化学有限公司	Improved method for synthesizing valsartan
EP2601180A1 *	2010-08-03	2013-06-12	Novartis AG	Highly crystalline valsartan
CN102060797A *	2010-12-31	2011-05-18	江苏江神药物化学有限公司	High-purity valsartanmethyl ester crystal production process
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CN102321038B *	2011-07-11	2014-03-26	安徽省虹升生物科技有限公司	Improved valsartan preparation method
CN103613558B *	2013-11-08	2015-10-21	浙江新赛科药业有限公司	A kind of preparation method of valsartan
CN103922528B *	2014-03-21	2019-07-02	浙江华海药业股份有限公司	A kind of method of Valsartan wastewater treatment
CN103923028B *	2014-05-04	2017-05-24	青岛雪洁助剂有限公司	Preparation method of valsartan methyl ester

* Cited by examiner, † Cited by third party, ‡ Family to family citation

Similar Documents

Publication	Publication Date	Title
CN101270096B	2011-08-03	Method for synthesizing diovan
CN103524440B	2015-09-09	The preparation method of gout therapertics Lesinurad and Lesinurad intermediate
CN105418460B	2017-04-12	Intermediate of pimavanserin and similar compound thereof, and preparation method thereof, and method for preparing pimavanserin and similar compound thereof
CN101817795B	2013-03-27	Improved method for synthesizing valsartan
CN103588657A	2014-02-19	Method for producing phenylacetamide compound
CN100575338C	2009-12-30	Compound of optically pure sulfenamides and application thereof
CN104557800B	2017-04-26	2-phenoxyl tetrahydrofuran (tetrahydropyrane) derivatives and application thereof in synthesis of penoxsulam
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CN110627736A	2019-12-31	Method for recycling 1-phenyl-5-hydroxy tetrazole
CN105523985A	2016-04-27	Preparation method of vildagliptin
CN104725292A	2015-06-24	Preparation method of (S)(-)-amisulpride
CN106883192B	2019-05-14	The synthetic method of the benzoic acid derivative of nitrogenous class heterocyclic antineoplastic pharmaceutical actives oxazolyl modification
CN102757390B	2015-04-22	Method for preparing 2-methoxy-4-diazanyl-5-fluoropyrimidine
CN105254611B	2017-10-31	The preparation method of the carboxylic acid of benzothiophene 2
CN105884625A	2016-08-24	Synthesis method of R-salmeterol
CN106966940B	2019-03-19	A kind of preparation method of Sitagliptin phosphate intermediate N arylmethyl -2S- cyano methyl acridine
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CN108658931A	2018-10-16	A kind of preparation method of Raltitrexed key intermediate

Priority And Related Applications

Priority Applications (1)

Application	Priority date	Filing date	Title
CN2007100383460A	2007-03-22	2007-03-22	Method for synthesizing diovan

Applications Claiming Priority (1)

Application	Filing date	Title
CN2007100383460A	2007-03-22	Method for synthesizing diovan

Legal Events

Date	Code	Title	Description
2008-09-24	C06	Publication	
2008-09-24	PB01	Publication	
2008-11-19	C10	Entry into substantive examination	
2008-11-19	SE01	Entry into force of request for substantive examination	
2011-08-03	C14	Grant of patent or utility model	
2011-08-03	GR01	Patent grant	
2013-12-18	ASS	Succession or assignment of patent right	**Owner name**: SHANGHAI INSTITUTE OF PHARMACEUTICAL INDUSTRY **Effective date**: 20131125
2013-12-18	C41	Transfer of patent application or patent right or utility model	
2013-12-18	C53	Correction of patent for invention or patent application	
2013-12-18	CB03	Change of inventor or designer information	**Inventor after**: Shi Huilin **Inventor after**: Wang Liquan **Inventor after**: Chen Wei **Inventor after**: Liu Dapeng **Inventor after**: Zhou Hu **Inventor after**: Tu Guoliang **Inventor before**: Wang Liquan **Inventor before**: Chen Wei **Inventor before**: Liu Dapeng

2013-12-18	COR	Change of bibliographic data	**Free format text**: CORRECT: INVENTOR; FROM: WANG LIQUAN CHEN WEI LIU DAPENG TO: SHI HUILIN WANG LIQUAN CHEN WEI LIU DAPENG ZHOU HU TU GUOLIANG
2013-12-18	TR01	Transfer of patent right	**Effective date of registration**: 20131125 **Address after**: 317024 flood bridge, Linhai City, Zhejiang **Patentee after**: Zhejiang Huahai Pharmaceutical Co., Ltd. **Patentee after**: Shanghai Institute of pharmaceutical industry **Address before**: 317024, Zhejiang province Linhai City Xun Town Li Zhuang **Patentee before**: Zhejiang Huahai Pharmaceutical Co., Ltd.
2015-12-09	C41	Transfer of patent application or patent right or utility model	
2015-12-09	CB03	Change of inventor or designer information	**Inventor after**: Wang Liquan **Inventor after**: Chen Wei **Inventor after**: Liu Dapeng **Inventor before**: Shi Huilin **Inventor before**: Wang Liquan **Inventor before**: Chen Wei **Inventor before**: Liu Dapeng **Inventor before**: Zhou Hu **Inventor before**: Tu Guoliang
2015-12-09	COR	Change of bibliographic data	
2015-12-09	TR01	Transfer of patent right	**Effective date of registration**: 20151117 **Address after**: 317024 flood bridge, Linhai City, Zhejiang **Patentee after**: Zhejiang Huahai Pharmaceutical Co., Ltd. **Address before**: 317024 flood bridge, Linhai City, Zhejiang **Patentee before**: Zhejiang Huahai Pharmaceutical Co., Ltd. **Patentee before**: Shanghai Institute of pharmaceutical industry

Concepts

machine-extracted

Download Filter table

Name	Image	Sections	Count	Query match
C09CA03 - Valsartan		title,claims,abstract,description	16	0.000
Valsartan		title,claims,abstract,description	16	0.000
valsartan		title,claims,abstract,description	16	0.000
synthesizing		title,claims,abstract,description	15	0.000
Diovan		title	1	0.000
chemical reaction		claims,abstract,description	18	0.000
sodium azide		claims,description	34	0.000
toluene		claims,description	34	0.000
triethylamine		claims,description	28	0.000
Pentaerythritol		claims,description	17	0.000
aromatic solvent		claims,description	16	0.000
solvent		claims,description	16	0.000
organic layer		claims,description	14	0.000
sodium chloride		claims,description	14	0.000

compounds	claims,description	13	0.000
acetic acid ethyl ester	claims,description	12	0.000
benzyl group	claims,description	12	0.000
water	claims,description	12	0.000
washing	claims,description	11	0.000
ester hydrochloride	claims,description	10	0.000
layer	claims,description	10	0.000
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4-Chlorotoluene	claims,description	9	0.000
potassium	claims,description	9	0.000
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potassium	claims,description	9	0.000
(N-propan-2-yloxycarbonylanilino) acetate	claims,description	8	0.000
HCl	claims,description	8	0.000
lithium	claims,description	8	0.000
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methyl group	claims,description	8	0.000
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hydrogen	claims,description	7	0.000
o-xylene	claims,description	7	0.000
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hydrogen	claims,description	6	0.000
hydrogen atoms	claims,description	6	0.000
salts	claims,description	6	0.000
substance	claims,description	6	0.000
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alkali	claims,description	5	0.000
alkyl group	claims,description	5	0.000
phenyl group	claims,description	5	0.000
preparation method	claims,description	5	0.000
Hydrazoic acid	claims,description	4	0.000
pentanoyl chloride	claims,description	4	0.000
acid	claims,description	3	0.000
crystallisation	claims,description	3	0.000
crystallization	claims,description	3	0.000
mixture	claims,description	3	0.000
precipitation	claims,description	3	0.000
stirring	claims,description	3	0.000

alkyl ester group	claims,description	2	0.000
cooling	claims,description	2	0.000
ethyl acetate extraction	claims,description	2	0.000
tolyl group	claims,description	2	0.000
ester hydrolysis	claims	1	0.000
hydrogen chloride	claims	1	0.000
hydrogen chloride	claims	1	0.000
separation method	claims	1	0.000
raw material	abstract,description	7	0.000
tin compounds	abstract,description	3	0.000
biosynthetic process	abstract,description	2	0.000
environmental pollution	abstract,description	2	0.000
synthesis reaction	abstract,description	2	0.000
industrial production	abstract	1	0.000

Show all concepts from the description section